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Class	Subclass

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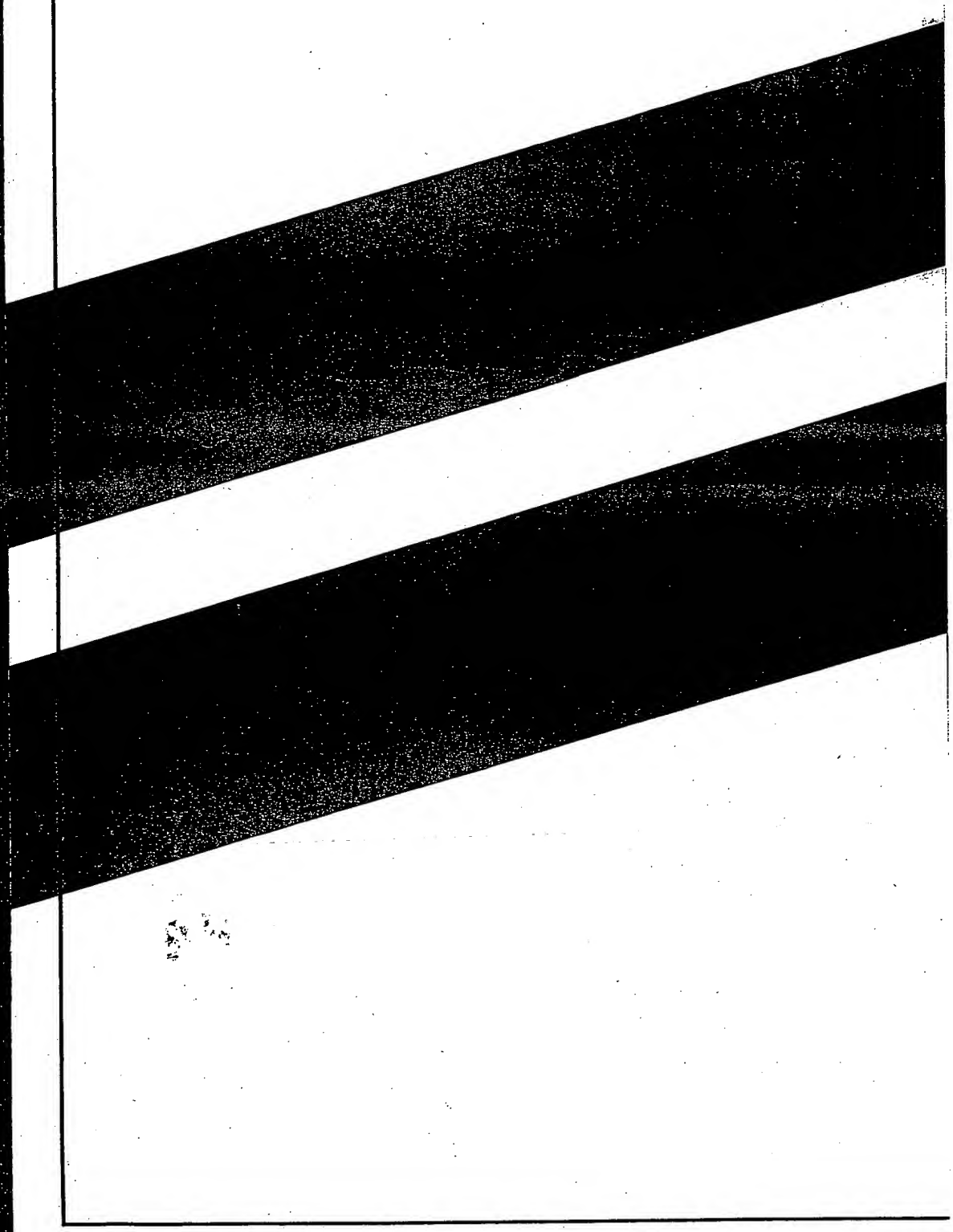

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SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
60/091,491 PROVISIONAL	07/02/98		0000	901.03.03

APPLICANT

KLAUS SODERMANN, LAHR, FED REP GERMANY.

CONTINUING DOMESTIC DATA********
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FOREIGN APPLICATIONS********
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Foreign Priority claimed 35 USC 119 (a-d) conditions met ☐yes ☐no ☐yes ☐no ☐Met after Allowance Verified and Acknowledged _____ Examiner's Initials	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
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ADDRESS

WILLIAMS & ASSOCIATES
1000 SIXTEENTH STREET NW
SUITE 701
WASHINGTON DC 20036-5741

TITLE

TAUROLIDINE/ACID COMPOSITION FOR USE AS AN ANTIBIOTIC LOCK

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
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FEE RECORD SHEET

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PTO-1556
(5/87)

ATTORNEY DOCKET NO. 901.03.03

IN THE U.S. PATENT AND TRADEMARK OFFICE
Provisional Application Cover Sheet

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Sir:

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (b)(2).

INVENTOR(s)/APPLICANT(s)

Last Name	First Name, MI	Residence (City and Either State or Foreign Country)
Sodemann	Klaus	77933 Lahr, Federal Republic of Germany

TITLE OF THE INVENTION

Taurolidine/Acid Composition For Use As An Antibiotic Lock

CORRESPONDENCE ADDRESS

Frederick C. Williams
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1401 New York Avenue, N.W.
Twelfth Floor
Washington, DC 20005, USA

ENCLOSED APPLICATION PARTS (check all that apply)

(X) Specification — *Number of Pages .. Cover plus 22* — (X) Small Entity Statements
( ) Drawing(s) — *Number of Pages .. None*
(X) Power of Attorney
( ) Additional inventors are being named on separately numbered sheets attached hereto.

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By Frederick C. Williams
Typed Name: Frederick C. Williams

Respectfully submitted,

Frederick C. Williams

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Date: July 2, 1998

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Paper No. #3

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In re Application of	
Sodemann	
Application Number: 60/091491	Filed: Jul 2, 1998
Art Unit	Examiner

Paper No. 4

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ATTORNEY DOCKET NO. 901.03.03

Application for United States Patent For:

TAUROLIDINE/ACID COMPOSITION FOR USE AS AN ANTIBIOTIC LOCK

Dr. Med. Klaus Sodemann
Lahr, Federal Republic of Germany

TAUROLIDINE/ACID COMPOSITION FOR USE AS AN ANTIBIOTIC LOCK

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a composition and method for the flushing and coating of catheters for the prevention of infection and blood coagulation.

2. Description of Related Art

Hemodialysis access systems for access to a human or animal patient's vascular system for exchange of blood between the vascular system and an external processing apparatus are well known in the art. Typically, a catheter is implanted in the patient with one end extending into the right-atrial region of the heart. As with any invasive procedure, the prevention of infection has been a problem, particularly with a device that must remain in place over protracted periods of time. Coagulation of the blood in and around the catheter has also proven troublesome and methods are needed for its prevention, particularly with regard to inhibiting the clogging of the catheter, which can diminish or destroy its usefulness. A significant amount of research has been directed to the alleviation of these problems.

It is standard procedure to flush catheters with an anticoagulant, such as heparin. However, heparin is not an antibacterial and, in addition, if not carefully controlled, it can carry the anti-coagulation process too far, thereby presenting a risk of hemorrhage.

U.S. Patent No. 4,096,241 discloses pharmaceutical compositions for the treatment and for prophylaxis of tooth and gum infections, and in particular parodontosis, comprising derivatives of thiadiazine as the active ingredient.

U.S. Patent No. 4,107,305 discloses a method of combating endotoxaemia by administering an effective amount of a taurolidine composition.

U.S. Patent No. 4,337,251 discloses the use of taurolidine in humans or animals to eliminate or reduce adhesions after surgery.

U.S. Patent No. 4,587,268 discloses a composition for the treatment of wounds comprising a resorbable aqueous gel having dissolved or dispersed therein one or more water-soluble medicaments, which are preferably an antibiotic or a methylol transfer antibacterial.

U.S. Patent No. 4,587,284 discloses the preparation of an enhanced water-absorbency hydrophilic polymer material, suitable for use in wound dressings by a process in which a water-containing organic hydrogel comprising a gelable polysaccharide and/or protein or polypeptide interspersed with a polymer of a hydrophilic acrylic or methacrylic acid derivative is permeated with a base, the pH of said hydrogel being raised to at least 9 during treatment with said base.

U.S. Patent No. 4,604,391 discloses the administration of taurolidine compounds prophylactically to humans or warm-blooded animals to combat the occurrence of osteitis or osteomyelitis, especially in patients suffering from bone injuries of traumatic origin.

U.S. Patent No. 4,626,536 discloses the use of taurolidine compounds to combat toxic proteins or peptides, e.g., venoms, fungal toxins and bacterial exotoxins, in the bloodstream of humans or warm-blooded animals.

U.S. Patent No. 4,772,468 discloses a pharmaceutical composition for filling into bone cavities comprising an aqueous paste formed from powdered calcium phosphate and an antibacterial substance, if necessary together with one or more binders. The antibacterial substance is preferably taurolidine and the calcium phosphate is preferably β-tricalcium phosphate.

U.S. Patent No. 4,797,282 discloses a drug depot, which can be implanted in the body, for the controlled, delayed release of cytostatics, comprising a synthetic material based on polyacrylates and/or polymethacrylates containing a cytostatic and at least one amino acid.

U.S. Patent No. 4,853,225 discloses an implantable medicament depot useful for combating infections comprising physiologically acceptable excipients and at least one delayed release active compound that is a chemotherapeutic of the gyrase inhibitor type.

U.S. Patent No. 4,882,149 discloses a pharmaceutical depot preparation for implantation into base tissue comprising natural bone mineral from which the naturally associated fat and bone-proteins have been removed whereby said bone is sterile and non-allergenic, said bone material having absorbed thereon and/or adsorbed therein one or more physiologically active substances. The physiologically active substance is advantageously an antibiotic or taurolidine or taurultam or a protein or polypeptide assisting bone regeneration.

U.S. Patent No. 4,905,700 discloses an acoustic coupling medium for transmitting ultra-sound . The medium, which is of use in ultrasonic visualization of the human body, comprises a sheet of hydrogel containing over 90% water, preferably over 95% water. The hydrogel preferably comprises agar, the chains of which are interspersed with chains of polyacrylamide.

U.S. Patent No. 4,960,415 discloses a device for inserting in wounds and wound cavities consisting of a container containing a pharmaceutically active substance, the walls of this container consisting at least partly of a membrane , preferably a semi-permeable membrane, which allows the active substance to escape into the wound area. The container is, more preferably, a dialysis tube. In order to drain off wound secretions, the container containing the pharmaceutically active substance, particularly taurolidine, is conveniently connected to a drainage

tube. Preferably, a drainage tube is used in which the end that leads into the wound is split into filaments.

U.S. Patent No. 5,077,281 discloses the use of taurolidine compounds as blood coagulation-inhibiting agents and as abacterial inflammation-inhibiting agents. According to the patent, taurolidine has outstanding coagulation-inhibiting action and is especially suitable for use in medical conditions requiring dialysis and for vascular prostheses. It is also disclosed that these compounds can be used together with other anti-coagulants such as coumarin or heparin.

U.S. Patent No. 5,167,961 and 5,417,975 disclose processes for the preparation of high purity bone mineral wherein the organic matter is degraded by heating with ammonia or a primary amine, characterized in that the solubilized degradation products are extracted by washing with flowing water at a temperature below 60° C., such heating with primary amine and washing steps optionally being repeated, whereby substantially all organic matter removable by these steps is removed, the bone mineral so treated being heated in air at temperatures up to 700 °C.

U.S. Patent No. 5,210,083 discloses an aqueous solution containing a bacterially effective concentration of taurolidine and/or taurultam together with a parenterally acceptable polyol. The aqueous solution is particularly suitable for parenteral administration.

U.S. Patent No. 5,362,754 discloses pharmaceutical compositions of a mixture of minocycline and EDTA (M-EDTA) and methods of using the compositions in maintaining the patency of a catheter port. Methods for inhibiting the formation of polysaccharide-rich glycocalyx (such as the glucocalyx of staphylococcal organisms) are also provided using an M-EDTA solution. The M-EDTA solution may also be used to pretreat a medical device to prevent adherence of infectious organisms, such as *S. epidermis* and *S. aureous*. The compositions

destroy and prevent the formation of polysaccharide-rich glycocalyx.

U.S. Patent No. 5,573,771 discloses a particulate bone mineral product for use in medicine, the particles of said mineral being substantially free from all endogenous organic material and having at least at the surface thereof resorbable, physiologically compatible, natural or synthetic macromolecular material. In particular, a bone mineral is provided that is impregnated with a gel-forming protein or polysaccharide such as gelatin to provide a surprising increase in strength and a product comprising bone mineral in a matrix of collagen-fibers and a gel-forming protein. Such products are intended as remodeling implants or prosthetic bone replacement.

U.S. Patent No. 5,593,665 discloses products containing tumor necrosis factor and taurolidine and/or taurultam as a combined preparation for simultaneous, separate or sequential use for treatment of patients suffering from medical conditions mediated by tumor necrosis factor.

U.S. Patent No. 5,603,921 discloses a medicated dental floss for controlling the bacterial activity associated with gingivitis. The floss incorporates an antimicrobial agent which, as a result of the flossing action, is deposited to the interdental area of the teeth. The slow dissolution of the antimicrobial agent ensures that effective levels of medication are attained for sustained periods, thereby reducing bacterial activity.

U.S. Patent No. 5,688,516 discloses compositions and methods of employing compositions in flushing and coating medical devices. The compositions include selected combinations of a chelating agent, anticoagulant, or antithrombotic agent, with a non-glycopeptide antimicrobial agent, such as the tetracycline antibiotics. Methods for using these compositions for coating a medical device and for inhibiting catheter infection are also disclosed.

Particular combinations include minocycline or other non-glycopeptide antimicrobial agent together with EDTA, EGTA, DTPA, TTH, heparin and/or hirudin in a pharmaceutically acceptable diluent.

Myers *et al., J. Appl. Bacteriol 48*:89-96 (1980) reported that taurolidine {Bis(1,1-dioxo-perhydro-1,2,4 thiadiazinyl) methane} is an antimicrobial compound formed by the condensation of two molecules of taurine with three of formaldehyde. It had been previously suggested that taurolidine releases formaldehyde in contact with bacteria. The authors presented evidence that indicated that taurolidine is mostly hydrolyzed in aqueous solution to release one molecule of formaldehyde and two monomeric molecules (1,1-dioxo-perhydro-1,2,4-thiadiazine and its carbinolamine derivative). A stable equilibrium was disclosed to have been established. The authors concluded that antibacterial activity was not entirely due to adsorption of free formaldehyde, but also to reaction with a masked (or latent) formaldehyde, as the activity of taurolidine was found to be greater than formaldehyde. The monomer was found to be only slightly active by comparison.

Gorman *et al., J. Clin. Pharm. Ther. 12*:393-399 (1987) reported on the examination of three antimicrobial agents, taurolidine, chlorhexidine, and povidone-iodine for microbial anti-adherence activity. Two adherence systems were investigated: an oral isolate of *Candida albicans* to human buccal epithelial cells and a urine isolate of *E. coli* to human uroepithelial cells. Each of the three agents exhibited significant anti-adherence activity, which was concentration dependent.

Root *et al., Antimicrobial Agents and Chemotherapy 32(11)*:1627-1631 (1988) reported that granulocytopenic patients with an intravascular catheter are at increased risk for infection

with *S. epidermis* and that during the intervals when the catheters are not being used for infusions, it is customary to maintain patency of the catheter lumen with a solution containing heparin. The authors showed that heparin does not inhibit the growth of *S. epidermis* isolated from the catheter of an infected patient. A 20-mg/mL solution of disodium EDTA, a chelating agent that effectively anticoagulates blood at this concentration, was shown to be bactericidal for an initial inoculum of 10^3 CFU of staphylococci per mL in 24 hours. Vancomycin, an antibiotic that is often employed to treat *Staphylococcus* infections was also found to be bactericidal for initial inocula of 10^3 CFU/mL at doses of 6.7 μg/mL, a drug concentration in the therapeutic range. The authors recommended that EDTA should be studied as a replacement for heparin solutions for the maintenance of intravenous catheters in granulocytopenic patients, in view of its low cost, effectiveness as an anticoagulant, and bactericidal activity.

Jones et al., J. Appl. Bacteriol. 71:218-227 (1991) examined the effects of three non-antibiotic, antimicrobial agents - taurolidine, chlorhexidine acetate, and providone-iodine - on the surface hydrophobicity of the clinical strains *E. coli, S. saprophyticus, S. epidermidis,* and *C. albicans.* At concentrations reported to interfere with microbial-epithelial cell adherence, all three agents were found to alter the cell surface hydrophobicity. However, these effects failed to exhibit a uniform relationship. Generally, taurolidine and povidone-iodine treatments decreased the hydrophobicity of the strains examined, whereas chlorhexidine acetate effects depended upon the micro-organism treated.

Traub *et al., Chemotherapy 39*:322-330 (1993) examined taurolidine for bactericidal activity against a representative number of multiple-antibiotic-resistant bacterial isolates in broth as well as in the presence of bovine and human serum and fresh defibrinated human blood. The

authors suggested that this antimicrobial substance might be employed for topical treatment of patients colonized or superficially infected by glycopeptide-resistant strains of *E. faecium*, *S. aureus* (GRMRSA), or by Enterobacteriaceae producing wide-spectrum β-lactamases.

Willatts *et al.*, *Crit. Care Med. 23(6)*:1033-1039 (1995) reported that taurolidine had no beneficial therapeutic effect on the outcome of patients admitted to the intensive therapy unit of a university teaching hospital with sepsis syndrome, using clinical, bacteriologic outcomes, progression of endotoxemia, resolution of organ failure, and 28-day mortality rate as end points.

In a talk presented at the 30th annual meeting of the American Society of Nephrology, held November 2-5, 1997 in San Antonio, Texas, Sodemann *et al.* reported on a four year trial of a gentamicin/sodium citrate mixture as an antibiotic-lock technique for salvage and prevention of catheter-related infections. They concluded that the replacement of catheters due to infection can be avoided by routine application of the concentrated gentamicin/citrate mixture and that even the salvage of intraluminally contaminated catheters is possible.

The disclosures of all of the foregoing are incorporated by reference herein in their entirety.

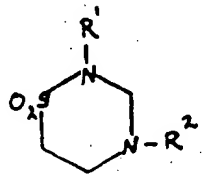
Notwithstanding the above-described contributions to the art, a need continues to exist for a safe and effective method for the prevention of infection and blood coagulation in patients whose illness requires the implantation of atrial catheters.

SUMMARY OF THE INVENTION

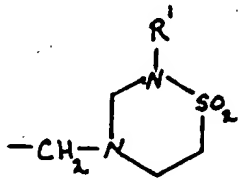
In accordance with the present invention, antibacterial/anti-coagulant compositions are provided for use in flushing and coating medical prosthetic devices, especially catheters.

More particularly, the present invention is directed to a method of inhibiting or preventing infection and blood coagulation in or near a medical prosthetic device after said device has been inserted in a patient comprising administering to the device a pharmaceutically effective amount of a composition comprising:

(A) at least one antibacterial compound of the formula



wherein R^1 is hydrogen or alkyl and R^2 is hydrogen or alkyl or a group of the formula

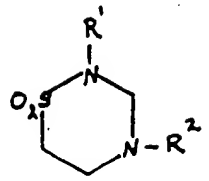


and

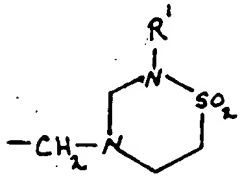
(B) at least one anti-coagulant selected from the group consisting of citric acid, phosphoric acid, ethylenediaminetetraacetic acid, ethylene glycol-bis-{β-aminoethyl ether}-N,N,N',N'-tetraacetic acid, and diethylenetriamine pentaacetic acid and biologically acceptable salts thereof.

In another embodiment, the present invention is directed to a medical prosthetic device coated with a composition comprising:

(A) at least one antibacterial compound of the formula



wherein R^1 is hydrogen or alkyl and R^2 is hydrogen or alkyl or a group of the formula



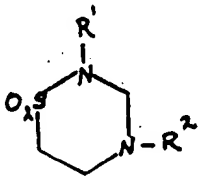
and

(B) at least one anti-coagulant selected from the group consisting of citric acid, phosphoric acid, ethylenediaminetetraacetic acid, ethylene glycol-bis-{β-aminoethyl ether}-N,N,N',N'-tetraacetic acid, and diethylenetriamine pentaacetic acid and biologically acceptable salts thereof,

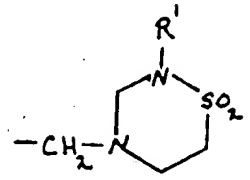
wherein the composition is included in a pharmaceutically effective amount for preventing or inhibiting infection and blood coagulation .

In still another embodiment, the present invention is directed to a medical prosthetic device prepared by a process comprising exposing the medical prosthetic device to a composition comprising:

(A) at least one antibacterial compound of the formula



wherein R^1 is hydrogen or alkyl and R^2 is hydrogen or alkyl or a group of the formula



and

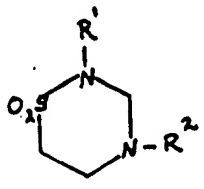
(B) at least one anti-coagulant selected from the group consisting of citric acid, phosphoric acid, ethylenediaminetetraacetic acid, ethylene glycol-bis-{β-aminoethyl ether}-N,N,N',N'-tetraacetic acid, and diethylenetriamine pentaacetic acid and biologically acceptable salts thereof,

wherein the composition is included in a pharmaceutically effective amount for preventing or inhibiting infection and blood coagulation .

DESCRIPTION OF THE PREFERRED EMBODIMENTS

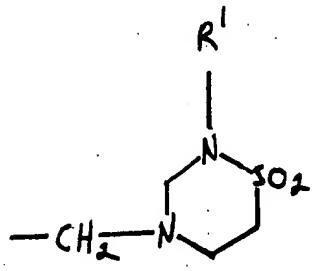
As stated above, the present invention is directed to a method of inhibiting or preventing infection and blood coagulation in or near a medical prosthetic device after said device has been inserted in a patient comprising administering to the device a pharmaceutically effective amount of a composition comprising:

(A) at least one antibacterial compound of the formula



I

wherein R^1 is hydrogen or alkyl and R^2 is hydrogen or alkyl or a group of the formula



II

and

(B) at least one anti-coagulant selected from the group consisting of citric acid, phosphoric acid, ethylenediaminetetraacetic acid, ethylene glycol-bis-{β-aminoethyl ether}-N,N,N',N'-tetraacetic acid, and diethylenetriamine pentaacetic acid and biologically acceptable salts thereof.

The preparation of representative examples of the compounds of formula I is described in U.K. Patent No. 1,124,285, which is incorporated herein by reference in its entirety..

Where R^1 and/or R^2 are alkyl, they may be either straight or branched alkyl and are preferably independently selected from those alkyls having from 1 to 8 carbon atoms, i.e., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and isomers thereof. More preferably, where R^1 and/or R^2 are alkyl, they are independently selected from those alkyls having from 1 to 6 carbon atoms, i.e., methyl, ethyl, propyl, butyl, pentyl, hexyl, and isomers thereof; most preferably, the alkyl group(s) have from 1 to 4 carbon atoms, i.e., methyl, ethyl, propyl, butyl, and isomers thereof. It is, however, most preferred that R^1 be hydrogen and that R^2 be hydrogen or a group of formula II.

In the present invention, of the compounds of formula I, the compounds taurolidine (R^1 =

H; R^2 = formula II) and taurultam ($R^1 = R^2$ = H) are particularly preferred. Taurolidine is bis-(1,1-dioxo-perhydroxy-1,2,4-thiadiazin-4-yl)methane. For convenience, hereinafter the compounds of formula I will be referred to simply as "taurolidine." Those skilled in the art will understand that taurultam and other compounds within the scope of formula I are also being referred to within the scope of the designation, unless the context dictates otherwise.

The antibacterial compound employed in the practice of the present invention is a formaldehyde carrier, i.e., a non-toxic derivative containing formaldehyde in combination.

The mode of action of taurolidine has been shown to include the transfer of methylol groups to hydroxyl or amino groups present on the above toxins or on the mureine of the bacterial cell walls. In solution, taurolidine exists in equilibrium with taurultam and N-methylol taurultam, taurolidine being greatly predominant. Taurultam is itself in equilibrium with methylol taurinamide, the equilibrium being greatly in favor of taurultam. When the above methylol derivatives, methylol taurultam and methylol taurinamide, contact the toxins or bacteria, methylol groups are transferred. Methylol taurultam is thereby converted to taurultam , while methylol tauramide is converted to taurine, a naturally occurring aminosulfonic acid that is extremely well tolerated in the human body. It will thus be appreciated that taurolidine and taurultam act in essentially the same way and produce the same final products.

Taurolidine and taurultam are condensation products of formaldehyde with taurinamide and are active not only against both gram-positive and gram-negative bacteria, but also against exotoxins and endotoxins produced by these organisms.

Bacterial infections by gram-negative organisms are commonly accompanied by endotoxaemia, that is, by the reaction of the patient to the endotoxin liberated by the organisms.

Endotoxin is a complex lipopolysaccharide constituent of the O-somatic antigen and is loosely attached to the cell walls of gram-negative bacteria. Irrespective of the bacterial source, all endotoxins exhibit similar toxic properties - in contradistinction to the exotoxins of gram-positive bacteria, which exert a wide range of individual effects. In man, it can produce the syndrome of endotoxin shock when large numbers of gram-negative bacteria are lysed. This syndrome is encountered in about 30% of patients with gram-negative septicaemia. It is known that endotoxins can be inactivated by taurolidine.

Toxic proteins, such as, exotoxins, can similarly be inactivated and methylol transfer antibacterials can be administered to combat toxic proteins in the absence of lipopolysaccharide toxins. Toxins that may be concerned include the exotoxins of such gram-negative bacteria as *E. coli* and *Bacteroides fragilis*. It is known that intravenous administration to mice of 0.2 mL of a 20% solution of taurolidine in sterile 5% polyvinyl pyrrolidone can very significantly reduce the mortality rate on intraperitoneal administration of pathogenic strains of both *E. coli* and *B. fragilis*.

Other toxic proteins include venoms such as mellitin and fungal toxins such as amanitin and α-bungarotoxin, which have been shown to be substantially detoxified by taurolidine.

A particular advantage of taurolidine is its very low toxicity; the intraperitoneal LD_{50} is mice is on the order of 1.5g/kg. As mentioned above, these compounds exhibit methylol transfer activity that results in the production of taurine, which is found naturally in the body and is particularly nontoxic.

A further advantage of taurolidine is its stability in aqueous solution, enabling the solutions to be pre-packed and stored over relatively long periods. Furthermore, it has been shown to be

non-teratogenic in mice.

Taurolidine will normally be administered as an aqueous solution by injection into the medical prosthetic device. Such solutions may contain, in addition to taurolidine, gentamycin sulfate or chondroitin sulfate and commonly contain a solubilizing agent, such as, polyvinyl pyrrolidone (PVP), to help maintain the taurolidine in solution and to contribute to the isotonicity of the solution.

Where PVP is incorporated into the solution, it will commonly be employed at a concentration in the range of from 4 to 7% by weight in order to achieve relatively high concentrations of those taurolidines that have low water solubility. The molecular weight of the PVP should not be greater that about 30,000 and is preferably less than 10,000, e.g., between about 200 and 3500. Kollidone® 17, sold by BASF is especially suitable. Such PVP is fairly quickly absorbed and excreted through the kidneys.

The amount of taurolidine solution injected into a medical prosthetic device will be enough to fill it. Such devices, when they are hemodialysis catheters, typically have internal volumes on the order of about 10 mL; the actual quantity will, of course, vary, for example, with the length of the tubing of the device, which, in turn, is, *inter alia,* a function of the size of the individual patient.

The concentration of taurolidine in such solutions is preferably in the range of from about 0.5 to about 5% by weight, depending, at the maximum, upon the solubility of the compound. Solutions of about 1.0 to about 2.0% taurolidine are particularly preferred.

An example describing the preparation of a stock solution of taurolidine has appeared in several patents, for example, U.S. Patent No.4,337,251:

15 Liters of double distilled pyrogen free water are filled into a 25 liter glass vessel with stirrer and intensive reflux device and heated to 50°C with stirring. Taurolidine (400 g) is added followed by PVP (Kollidone 17; 1000g). After dissolution, the solution is cooled and the pH adjusted to 6.0 with a few drops of 0.1 N hydrochloric acid. The solution is then passed through an adsorption filter to remove microorganisms and pyrogens and through a sterilizing Millipore filter before being filled into 100 mL vials, which are finally autoclaved.

If desired, some or all of the PVP may be replaced by a parenterally acceptable polyol. This use for polyols has been disclosed in U.S. Patent No. 5,210,083, the disclosure of which is incorporated herein by reference in its entirety. There, it is pointed out that at higher concentrations of taurolidine, crystallization can occur, which can render the solution unuseable.

It will be noted that in the above-described procedure, the pH is lowered to 6.0. Although taurolidine can be used on the basic side of neutral, e.g., about pH 8, it has been found to be more effective when used on the acidic side. Typically, the combined antibacterial and anticoagulant composition of the present invention will have a pH in the range of from about 3.5 to about 6.5, preferably from about 4 to about 6 and, most preferably from about 5 to about 6. The composition will normally be at a physiological pH. If necessary, the pH can be adjusted by additional acid, such as a mineral acid, for example hydrochloric acid, or, preferably, one that will not cause acidosis, such as, for example, acetic, malic, or lactic acid, or a physiologically acceptable buffer, for example, primary potassium citrate, acetic acid-sodium acetate, potassium acid phthalate-sodium hydroxide, secondary sodium citrate, and the like. Other methods for adjusting the pH, familiar to those of skill in the art, can also be employed, such as, for example, McIlvaine's standard buffer solutions, which are prepared using varying ratios of a stock solution

of 0.1 molar citric acid and a stock solution of 0.2 molar disodium phosphate.

In the case of bacteria and their endo- and exotoxins, it has been found that after the methylol transfer, as described above, there is a further irreversible step involving dehydration. Thus, in the case of bacterial endotoxins, which are lipopolysaccharides, it was found that an irreversible cross-linking reaction takes place that prevents the endotoxin from exerting its lethal effect. Similarly, in the case of bacterial exotoxins, which are proteins or polypeptides and do not contain lipopolysaccharide material of the kind found in the endotoxins , the detoxification reaction has been found to be irreversible. However, it is disclosed in U.S. Patent No. 5,210,083 that the transfer of methylol groups by the mechanism set out above is reversible in the case of many hydroxyl or amino compounds, so that an equilibrium can be established that does not significantly interfere with the availability of taurolidine. Thus, polyols, such as, sugars and sugar alcohols, can also be used to maintain relatively high concentrations of taurolidine and/or taurultam in aqueous solution without significantly affecting their antibacterial and antitoxin activity. Preferred polyols include carbohydrates, e.g., hexoses, such as, glucose, fructose, and mixtures thereof; pentoses, such as, xylose; polysaccharides, such as, dextran or hydrolyzed starch; glycerol; and sugar alcohols, such as, sorbitol, mannitol, and xylitol. Glucose is most preferred.

The concentration of the polyol is typically in the range of from about 3 to about 40% by weight. In the case of glucose, the concentration is preferably in the range of from about 10 to about 30% by weight, more preferably about 20%.

Where such polyols are used, the concentration of taurolidine in the solution is preferably in the range of from about 1 to about 5%, more preferably in the range of from about 2 to about

3% by weight. The concentration of taurultam is preferably in the range of from about 1 to about 7.5%, more preferably in the range of from about 3 to about 5% by weight.

Since gram-negative organisms will frequently be present and since the bacteriostatic activity of taurolidine is lower than that of many conventional antibiotics, it is often advantageous to administer the compositions employed in the practice of the present invention in conjunction with a broad spectrum antibiotic substance, more especially, a substance strongly active against both gram-positive and gram-negative pathogens that, preferably, induces no or only delayed resistance, for example, a β-lactam antibiotic, such as, penicillin, ampicillin, or cephalosporin; a tetracycline antibiotic; a macrolide antibiotic, such as, erythromycin; a polypeptide antibiotic, such as, bacitracin or novobiocin; or, more preferably, an aminoglycoside antibiotic, such as, amikasin, butirosin, fortimycin, streptomycins, neomycin, linkomycins, such as, clindamycin and lincomycin, kanamycin, dideoxykanamycin B (DKP), lividomycin, netilmicin, ribostamycin, sagamycins, seldomycins and their epimers, sisomycin, sorbistin, tobramycin, vancomycin, gentamicin, and rifamycins, such as, rifampicin and rifamycin; and the like. Of these, gentamicin is preferred.

However, antibiotics are often contraindicated for use in surgical treatment, owing to their tendency to produce resistant strains. Taurolidine's bacteriostatic activity is not generated by the same mechanism as is that of the antibiotics and, thus, does not bring about the production of such resistant strains. Therefore, in a given case, it may be preferable to rely solely on the taurolidine for antibacterial action.

The composition employed in the practice of the present invention preferably also contains a pharmacologically acceptable carrier solution, such as, water, Ringer's solution, or saline.

Additionally, the compositions of the present invention can also contain other dissolved additives that can favorably influence their physical and biochemical properties, for example, amino acids, sugar, common salt, and the like.

The antibacterial compositions of the present invention are used in combination with an anticoagulant. U.S. Patent No. 5,077,281 teaches that taurolidine compounds exhibit outstanding coagulation-inhibiting action in their own right and are especially suitable for use in medical conditions requiring dialysis and for vascular prostheses, either alone or in combination with other anti-coagulants such as coumarin or heparin. Contrary to the teaching of U.S. Patent No. 5,077,281, "Taurolin", published by W. L. Bruckner and R.W. Pfirrmann, Verlag Urban und Schwarzenberg, Munich, 1985, expressly states that taurolidine does not influence blood coagulation and displays no anti-phlogistic action. It appears that taurolidine does, in fact, exhibit anti-coagulation properties, but not to the extent that, for example, heparin does. Thus, it has been found by the present inventors that the addition of certain other anti-coagulants can be beneficial for enhancing the effect where taurolidine is being used, without going to the levels exhibited by heparin, which, as noted above, can be dangerous.

In accordance with the present invention, beneficial results are achieved when the antibacterial taurolidine is combined with a blood coagulating amount of an acid selected from the group consisting of citric acid, phosphoric acid, ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis-{β-aminoethyl ether}-N,N,N',N'-tetraacetic acid, and diethylenetriamine pentaacetic acid and biologically acceptable salts thereof. It is preferred that the acid employed in the practice of the present invention be an organic acid, especially one having at least one carboxyl group, particularly citric acid or EDTA. It will be understood that the addition of one or more of these

acids may, by itself, act to lower the pH of the composition to a level at which no other pH regulator, e.g., a buffer, is required.

EDTA is a known anticoagulant that is used in blood collection tubes. It is also known to have the ability to form chelates with calcium. Since calcium is one factor that is known to have a role in the coagulation of blood, it is believed possible that at least part of EDTA's efficacy in anticoagulant activity may be brought about by this means. Sodium citrate is also believed to have anticoagulation properties by virtue of its ability to generate insoluble calcium citrate.

Ethylene glycol-bis-{β-aminoethyl ether}-N,N,N',N'-tetraacetic acid (EGTA) and diethylenetriamine pentaacetic acid (DTPA) and salts thereof are other known chelating agents that can be used in place of, or in addition to, EDTA or citric acid/citrate.

The foregoing anticoagulants can be used in the free acid state, but, more often will be employed with one or more of their carboxylic acid groups neutralized with an appropriate base. Generally, it will be desirable to employ a cation that will form a salt that is soluble in aqueous solution, such as alkali metal ions, e.g., sodium, potassium, or lithium. Zinc citrate may also be employed. Sodium or potassium salts are normally preferred, especially sodium, and the disodium salt of EDTA and sodium citrate and most preferred.

The acid and/or salt will be used in a concentration effective to bring about the desired anticoagulation effect and may, at the same time, as mentioned above, bring about, or help to bring about, an appropriate pH for biological use.

Although the process of the present invention is primarily concerned with introducing the antibacterial/anticoagulant compositions into catheters that are already in place, those skilled in the art will understand that contacting an artificial surface outside the body with these

compositions can prevent the deposition of blood coagula on such surface after its implantation. Thus, the surfaces of medical devices, such as hemodialysis catheters, can be pre-treated by the compositions employed in the practice of the present invention to prevent the blockage due to blood coagula that presents a favorable site for bacteria growth and thereby prevent the infection that may ensue. The apparatus can be treated with a dilute, say, 3%, solution of the composition initially and then, after insertion, with repeated periodic flushing as referred to above.

Although the process of the present invention is primarily and preferably directed to maintaining the patency and asepsis of implanted hemodialysis catheters, beneficial effects may also be obtained in applying the process to other, similar devices, such as, central venous catheters, peripheral intervenous catheters, arterial catheters, Swan-Ganz catheters, umbilical catheters, percutaneous nontunneled silicone catheters, cuffed tunneled central venous catheters as well as with subcutaneous central venous ports.

Various features and aspects of the present invention are illustrated further in the examples that follow. While these examples are presented to show one skilled in the art how to operate within the scope of the invention, they are not intended in any way to serve as a limitation upon the scope of the invention.

EXAMPLE

A 0.5% solution of taurolidine in Ringer-lactate solution (Thomae, Biberach, Germany) was introduced into each of four polyethylene bottles having a 30 mL volume. Filling volumes were 5, 10, and 15 mL. One bottle was filled with 5 mL of the taurolidine solution and 2 mL ACD-A (Fresenius, Bad Homburg, Germany) solution. ACD-A solution is used for the

conservation of whole blood and contains per liter: 22.0 grams of sodium citrate dihydrate, 7.3 grams of citric acid and 34.5 grams of glucose monohydrate.

Blood was collected at the slaughter house from a female pig directly from the slaughter wound into the containers that were then filled up to the 30 mL level. The containers were capped and gently moved to mix blood with the solution. The containers were inspected after 30 minutes. Blood in the containers containing only taurolidine was clotted, but the blood in the container containing the mixture of taurolidine and ACD-A was not clotted. Thus, it is concluded that the addition of citric acid to taurolidine can increase the level of anti-coagulation, as is desired.

POWER OF ATTORNEY

POWER OF ATTORNEY FOR PATENT APPLICATION	ATTORNEY DOCKET NO. 901.03.03

I, Klaus Sodeman, the sole inventor of the PATENT APPLICATION entitled:

Taurolin/Acid Composition For Use As An Antibiotic Lock

the specification of which is attached hereto, hereby appoint the following attorney listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Frederick C. Williams, Reg. No. 36,969

Send Correspondence to: Frederick C. Williams Williams & Associates 1401 New York Avenue, N.W. Twelfth Floor Washington, DC 20005	Direct Telephone Calls To: (202) 842-0431 Frederick C. Williams

Full Name of Inventor: Dr. Med. Klaus Sodemann K.S. **Citizenship:** German

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[signature]

Klaus Sodemann K.S.

6/30/1998

Date

Attorney Docket No: 901.03.03

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27(b)) - INDEPENDENT INVENTOR

I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled:

Taurolin/Acid Composition For Use As An Antibiotic Lock

described in
(X) the specification filed herewith with title as listed above.
( ) application serial no. __ filed __.
( ) patent no. __ issued __.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a non-profit organization under 37 CFR 1.9(e).

Each person concern, or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

( ) No such persons, concerns, or organizations exist.
(X) Persons, concerns, or organizations are listed below:

Name Biolink Corporation
Address 47 East Grove Street
Second Floor
Middleboro, MA 02346

( ) Individual
(X) Small Business Concern
( ) Nonprofit Organization

Name ____
Address ____

( ) Individual
( ) Small Business Concern
( ) Nonprofit Organization

Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing from thereon, or any patent to which this verified statement is directed.

Dr. Med. Klaus Sodemann
NAME OF INVENTOR

K. Sodemann Signature of Inventor

6/20/1998
Date

Attorney Docket No: 901.03.03

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

( ) the owner of the small business concern identified below:
(X) an official of the small business concern empowered to act on behalf of the small business concern identified below:

Name of Small Business Concern: Biolink Corporation
Address of Small Business Concern: 47 East Grove Street, Second Floor
Middleboro, MA 02346

I hereby declare that the above identified concern qualifies as a small business concern as defined in 13 CFR 121.1301 through 121.1305, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled Taurolidine/Acid Composition For Use As An Antibiotic Lock,
by inventor(s) Klaus Sodeman,

described in (X) the specification filed herewith with title as listed above.
( ) application serial no. filed .
( ) patent no. __ issued __.

If the rights held by the above identified small business concern are not exclusive, each individual, concern, or organization having rights to the invention is listed below and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

(X) No such persons, concerns, or organizations exist.
( ) Persons, concerns, or organizations are listed below:

Name _____	Name _____
Address _____	Address _____
_____	_____
( ) Individual	( ) Individual
( ) Small Business Concern	( ) Small Business Concern
( ) Nonprofit Organization	( ) Nonprofit Organization

Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Frank R. Prosl

TITLE OF PERSON IF OTHER THAN OWNER President

ADDRESS OF PERSON SIGNING 47 East Grove Street , Second Floor, Middleboro, MA 02346

SIGNATURE Frank R Prosl DATE 6/23/98

9200/109-00

PROVISIONAL PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Provisional Application of

KLAUS SODEMANN

Serial No.: 60/091,491

Filed: July 2, 1998

For: TAUROLIDINE/ACID COMPOSITION FOR USE AS AN ANTIBIOTIC LOCK

Group Art Unit:

Examiner:

Hon. Assistant Commissioner for Patents
Washington, DC 20231

Sir:

NOTICE OF CHANGE OF ADDRESS

Please take notice that undersigned counsel of record for Applicant(s) has changed his official address to

Williams & Associates
1000 Sixteenth Street, N.W.
Suite 701
Washington, DC 20036-5741

The voice telephone number remains (202) 842-0431, but the FAX number has changed to (202) 467-4045. Thank you for your assistance in this matter.

Respectfully submitted,

Frederick C. Williams

Frederick C. Williams
Reg. No. 36,969

CERTIFICATE OF MAILING

I hereby certify that the attached paper or fee is being deposited with the United States Postal Service, postage prepaid, on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

Frederick C. Williams
Name of Person Mailing

Frederick C. Williams
Signature of Person Mailing

October 1, 1998
Date

1614

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Application

Address to:
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Application Number	60/091,491
Filing Date	7/2/1998
First Named Inventor	Sodemann
Group Art Unit	1614
Examiner Name	Weddington, K. E.
Attorney Docket Number	901.03.03-P

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I am the:

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☐ Assignee of record of the entire interest.
Certificate under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ Attorney or agent of record.

☐ Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number _____

Typed or Printed Name	Frederick C. Williams Reg. No. 36,969
Signature	Frederick C. Williams
Date	February 28, 2001

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than on signature is required, see below*.

☒ *Total of 1 39 forms are submitted.

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